# American Journal of Pharmacy

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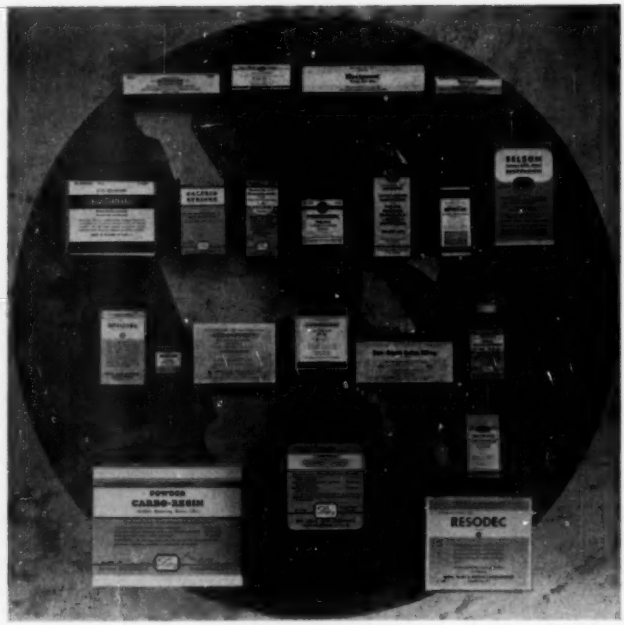


NEW DRUGS
(See review beginning this issue)

Since 1825 October 1951

AMERICAN JOURNAL OF PHARMACY VOL. 123 OCTOBER 1951 NO. 10

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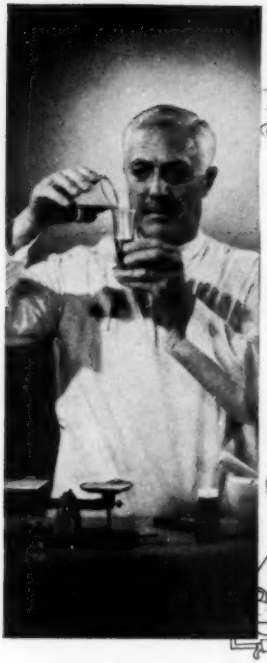

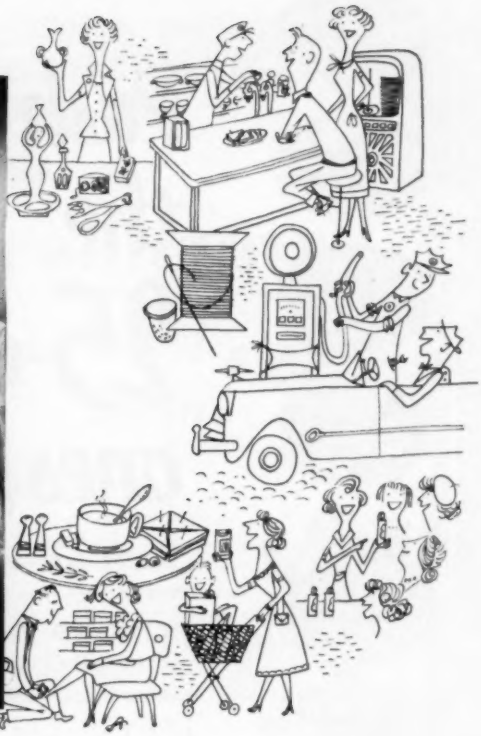

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# AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825



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Vol. 123 OCTOBER 1951 No. 10


## CONTENTS


**Editorial**

Progress and Price ..... 318

**Article**

Current Trends in Modern Medicinals (Part I). By Madeline O. Holland ..... 321

# E D I T O R I A L

## PROGRESS AND PRICE

THE two most common criticisms of modern pharmacy are that the pharmacist, today, has little challenge in his work and that prescriptions cost too much. The first of these is sometimes directed at pharmacy by pharmacists themselves while the latter is a criticism of laymen. In both instances it stems from a narrow and warped appraisal of the true facts.

The pharmacist of a few decades ago was called upon to compound all sorts of strange mixtures and combinations and it was with a great sense of achievement and satisfaction that he blended the ingredients into a clear solution or a carefully suspended mixture, whichever resulted. Rarely, if ever, did he appreciate or even know whether the end product was pharmacologically active or inert; after all his task was accomplished. Actually, from the patients' standpoint it mattered little, for physicians with the drugs of that time could achieve little in the way of cures. Palliation of pain, relief of fever and sympathy were the physician's chief contribution; nature alone accomplished the real conquest of disease. How different, today, now that we have specifics for dozens of infectious and other maladies that afflict man.

Consider the single disease, pneumonia, which once was fought with antipyretics and sometimes digitalis for the failing heart. The patient who survived the crisis recovered; he who could not succumbed. Today, the physician may choose any one of several antibacterial agents which take much of the hazard from this once foremost killer of men and women in the prime of life. The same could be said of many other diseases wherein specifics are available that make treatment both simple and effective.

The question is, did the pharmacist of old, when he compounded and dispensed an antipyretic, cataplasma of kaolin, and all the other worthless material for the pneumonia patient, really achieve more and render more help than, today, when he dispenses 16 capsules which

are an almost certain cure? Is his service to humanity less today than before and would anyone wish to return to those "good old days"?

Pharmacists in this modern era should derive great satisfaction in the knowledge that it is their prescription, more than anything else, including the physician's skill, that saves the patient's life and restores his health.

Surely both the medical profession and the public are fully aware of the primary importance which our modern drugs play in improving health and longevity. Why pharmacists need be apologists for their custodianship of miracles is hard to understand. Quite possibly, the retail pharmacist fails at times to appreciate the fact that he is an integral part of the pharmaceutical team which makes these miracle drugs available. It is surely true that the pharmacist, almost invariably, fails to appreciate his growing challenge and responsibility in giving guidance to the medical profession in the selection and use of drugs, and to the public on general health matters. Both of these needs exist and the pharmacist who is prepared and willing will find both physicians and the public seeking his advice.

The high cost of prescriptions is a criticism stemming largely from our poor public relations. Such an accusation is indeed an anomaly in view of the well established fact that pharmacists rarely charge half as much for their time as plumbers!

Today's specifics are the products of extensive and costly research. A drug like aureomycin, for example, came only after years of exhaustive research, and for each such "find" there are hundreds of failures requiring just as much effort. Not only must the cost of such research be amortized but production and control continues to be costly.

The true way of assessing the cost of a modern drug is to evaluate the total cost of some illness today as compared with years ago. Here again, pneumonia is a typical example. Some few years ago the pneumonia patient was critically ill for days followed by a long convalescence. The total cost including medical and nursing care, loss of working time, and drugs was many times that of today even at today's inflated prices. Furthermore, the death rate in pneumonia was many times that of today and who can assess the value of a loved one's life? Actually, illness, today, is less expensive than ever, although the cost of drugs takes more of the total spent for medical care

than previously. This is as it should be for drugs are more important than ever and their production more complex and costly.

Pharmacists have reason to be proud of their part in the conquest of disease. Changing times have not minimized our importance but made pharmacy's service indispensable. The old apothecary shop had its aroma and mystery but its products were only one step removed from the incantations of the ancient priests and medicine men. We should be proud of our scientific progress and sound achievement and look to the future for still greater strides ahead. The conquest of all diseases and possibly the conquest of aging itself should be our goal. In striving toward it we must not drag our feet and longingly look behind.

L. F. Tice

# CURRENT TRENDS IN MODERN MEDICINALS

## (Part I)

By Madeline O. Holland,* D. Sc.

REFLECTED in this annual review of progress in the various fields related to public health is the progress accomplished in the last year in new drugs and technics. Although many of the compounds described may still be undergoing animal experimentation or preliminary clinical trials, the results of which may lead to their abandonment, they are indicative of possible present and future trends.

## ADRENERGIC BLOCKING DRUGS

### Flaxedil

Tri-(diethylaminoethoxy) benzene triethyliodide is a a new well-tolerated curare-like compound which has shown value in surgical and nonsurgical procedures which require muscular relaxation. It has all of the advantages of natural curare, but it is claimed to be easier to administer and less apt to be followed by disturbing reactions.

It acts by relaxing the skeletal muscles and its progressive action is similar to that of curare. It may be used in abdominal surgery; operations upon the thorax and adjacent structures; in arthroplasty and reduction of dislocations or fractures; for operations about sphincters; in suprapubic prostatectomy; for endoscopic exploration and for tracheal intubation. This new drug also may be used for the prevention of accidents during shock therapy in psychiatric cases, and for relaxing spastic muscles during non-operative orthopedic procedures.

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* Editor, *American Professional Pharmacist;* Technical Editor, *El Farmaceutico* and *Pharmacy International.*

In a recent study on 42 anesthetized patients this drug, given in single intravenous doses of 0.5, 1.0, 1.5 and 2.0 mg/Kg. reduced the respiratory minute volume (RMV) to 90 percent, 70 percent, 30 percent and 10 percent of control respectively. The depression reached a maximum in five minutes. The average duration of the action following doses of 1-2 mg./Kg. was 40 minutes. A cumulative effect was observed when a second dose was given after the RMV had returned to the control level. The only side effect observed was a sinus tachycardia which persisted beyond the time of the neuromuscular blockade.

Under the name of Flaxedil, tri-(diethylaminoethoxy) benzene triethyliodide is available in multiple dose vials of 20 cc. containing 20 mg. per cc. from Lederle Laboratories Division, American Cyanamid Company.

**SKF 688**

At a recent meeting of the American Society for Pharmacology and Experimental Therapeutics, there was described a new effective and orally-active adrenergic blocking agent. Chemically, it is N-phenoxyisopropyl-N-benzyl-β-chlorethylamine. It is related to Dibenamine.

Animal studies have shown that this drug and other members of its family possess the unique ability of blocking a basic action of adrenalin, namely, its narrowing effect on the peripheral vascular system (blood vessels of the limbs and many of the smaller vessels of the body). Of the various drugs studied N-phenoxyisopropyl-N-benzyl-β-chlorethylamine has shown the greatest oral effect. The constriction of the peripheral vascular system by extra quantities of adrenalin either secreted or injected causes a rise in blood pressure. However, if a drug of this type is given first the constriction is prevented, and the blood pressure rises only slightly or not at all. The investigators of this drug and related compounds believe that these drugs do not act directly on the body but rather limit the effect of adrenalin.

Although Dibenamine is an effective adrenergic blocking agent, research has been directed towards synthesizing such an agent which would be effective at a lower dosage so as to overcome side-effects, but which would be sufficiently active when taken by mouth in order to be of practical value for long-term use.

Tests with animals of both the intravenous and oral activity of the various related compounds revealed no correlation between the two routes but did reveal the superiority of N-phenoxyisopropyl-N-benzyl-β-chlorethylamine.

Arterial volume pulse measurements made on various arteries showed that the drug itself had little or no effect on blood pressure, and that it acted rather by limiting the constrictor effect of adrenalin. The drug was found to reach its full effect two to three hours after dosage, and to remain considerably effective up to 48 hours later.

Toxicity tests showed that the drug is safe for human beings. It does cause vomiting at the same dosage level as Dibenamine, but since it is effective at a lower dosage level it is possible that it can be given without causing this side effect. Thus, it is now undergoing clinical trial.

When given intravenously, compounds of this series containing bromide were more active than similar chlorine compounds, but the opposite was true when they were given orally. This difference is believed to be determined by the speed with which the drugs react with other elements in the body and thus lose their potency. The "chloro" types retain their original form longer and thus seem to be absorbed into the system in active form, whereas the "bromo" types are altered too rapidly when given orally. But, given intravenously, the "bromo" types apparently have time to act before being inactivated, and on this basis show superiority over the other form.

Under the laboratory name of SKF #688 this drug is being investigated by Smith, Kline and French Laboratories.

**Win 2747**

A new curarimetric drug being studied is 2, 5-bis-(3-diethylaminopropylamino)-benzoquinone-bis-benzylchloride, or Win 2747. In comparison with d-tubocurarine chloride pentahydrate in rabbits it was found that the duration of curarimetric activity in mice and rabbits was about the same for both substances. Its activity was about five times that of d-tubocurarine, but about four times as toxic when given intravenously. Subcutaneously this new agent was only one-half as active and one-fourth as toxic as d-tubocurarine. As Mytolon Chloride this drug is available from Winthrop-Stearns, Inc.

## ANALGESICS

### Butamed

n-Butyl alcohol is a colorless liquid with a pungent odor, having a specific gravity of 0.810 at 20°/4°C. It solidifies at 79.9°C. and boils at 117°C. It mixes freely with alcohol and ether and is soluble to the extent of 7.9 parts in 100 parts of water at 15°C.

Since animal experiments showed a relative lack of toxicity for n-butanol it was given in a saturated saline solution to humans. It was given both intramuscularly and intravenously. Orally n-butanol was administered in the form of a saturated water solution diluted to taste. A large number of individuals have been tested with these solutions. When given intramuscularly or subcutaneously the dosage employed was 2-10 cc. In some instances as much as 50 cc. were given intramuscularly at one time. For the intravenous studies a group of 100 post-operative patients was selected. The n-butanol was given in quantities of 2,000 cc. of a 0.2 percent solution in five percent glucose or in saline at a rate of 60 drops per minute. When given orally it was found that doses as high as 80 cc. of the saturated solution could be given to some subjects. No undesirable side effects have been revealed thus far in humans. There are no noticeable alterations in pulse rate, blood pressure and respiration.

Clinical trials of n-butanol have shown that it relieves a number of types of pain. Thus far these include the following: (a) post-operative pain due to surgical trauma; (b) pain accompanying diagnostic procedures such as proctoscopy, cystoscopy, etc.; (c) traumatic pain-lacerations, contusions, fractures; (d) myalgias; (e) osteoarthritis; (f) burns, sunburn; and (g) dysmenorrhea.

Although the mechanism by which n-butanol acts in preventing or controlling immediate shock from severe extensive burns is not known definitely it appears that its pharmacological action may influence fundamental biochemical changes occurring as a result of cellular damage. It does not appear to influence blood volume since no edema of the burned tissues occurred.

It is hoped that this effect of n-butanol may find application in saving lives of persons who may be severely burned.

### Dromoran Hydrobromide

A new synthetic analgesic known chemically as *dl*-3-hydroxy-N-methylmorphinan hydrobromide is now recommended for the relief of

severe pain, especially in tumors, biliary and renal colic, myocardial infarction, bursitis, neuritis and for preoperative and post operative pain relief. Tests have shown it to be much more potent and longer-acting than morphine when given subcutaneously. Its margin of safety is higher than that of methadone, being approximately the same as morphine. It is a narcotic and under the tradename of Dromoran is supplied by Hoffman-LaRoche.

**Isomethadone and Ketobemidone**

Isomethadone and Ketobemidone are two derivatives of methadone which are still under investigation. There is considerable controversy over their respective potencies and analgesic properties. Ketobemidone has been found to cause addiction to the same degree as heroin. This would seem a serious drawback to its use.

They are being investigated by Winthrop-Stearns.

**Nucodan and Percodan**

To meet the needs of an analgesic stronger than codeine, but less potent than morphine, dihydro-hydroxycodeinone, a new codeine derivative has been introduced.

It is marketed by Endo Products, Inc., in two different forms under the brand names Percodan and Nucodan.

Each Percodan tablet contains:

| | |
|---|---|
| Dihydrohydroxycodeinone hydrochloride | 4.50 mg. |
| Dihydrohydroxycodeinone terephthalate | 0.38 mg. |
| Homatropine terephthalate | 0.38 mg. |
| Acetylsalicylic acid | 224 mg. |
| Acetophenetidin | 160 mg. |
| Caffeine | 32 mg. |

Each Nucodan tablet contains:

| | |
|---|---|
| Dihydrohydroxycodeinone hydrochloride | 4.50 mg. |
| Dihydrohydroxycodeinone terephthalate | 0.38 mg. |
| Homatropine terephthalate | 0.38 mg. |
| Pentylenetetrazol | 50 mg. |

Percodan is especially indicated in all cases of acute pain, Nucodan in chronic conditions or in cases of heart and respiratory disease. Nucodan contains pentylenetetrazol, an antidote for opium derivatives, which counteracts certain undesirable effects on opiates.

### Salicylamide

A new analgesic, salicylamide, is claimed to have more than seven times the pain-killing potency of aspirin and twice as much as antipyrine. In contrast to other salicylates, salicylamide consistently was well tolerated in high dosages in addition to proving very effective in reducing pain and fever. Particularly favorable results were noted in treatment of rheumatic disorders affecting the muscles, ligaments and joints. Undesirable side effects caused by aspirin such as digestive disturbances and dizziness were not noted in patients who had poor tolerance for aspirin who were given high dosages of salicylamide.

Salicylamide is available to the pharmaceutical industry in commercial quantities from Heyden Chemical Corporation and Chemo-Puro.

### N-(2-(2-pyridyl)-ethyl phthalimide

A new pain killer for severe menstrual conditions and headaches has been reported. Chemically it is N-(2-(2-pyridyl)-ethyl-phthalimide. In experiments with laboratory animals, the new analgesic was found to be three times more effective than aminopyrine also known as Pyramidon. Unlike aspirin, the new pain-killer does not reduce fever. It is twice as active in decreasing the stimulation induced by such drugs as desoxyephedrine.

This new drug is being investigated by the Sterling-Winthrop Research Institute.

## ANESTHETICS

### Xenon

Xenon is the inert gas employed to produce the purple color in advertising signs. However, it has now found use as a surgical anesthetic. It appears to be safer than most anesthetic gases during administration because there is no danger of explosion and fire. It produces rapid anesthesia and recovery with no ill effects.

## ANTIBIOTICS

### Aerosporin

Polymyxin B is obtained from the organism *Bacillus polymyxa* also known as *Bacillus aerosporus* Greer. The purified drug is a creamy white powder. It is standardized biologically against the Official Polymyxin Standard which, for convenience is assigned the potency of 10,000 Units per milligram. Polymyxin B consists of γ, 2-diaminobutyric acid, several amino acids and a fatty acid so far unidentified. The five known polymyxins are distinguished chemically by variations in their amino acid content.

It is very stable, solutions will retain their potency for at least two weeks, even at room temperature. Boiling for ten minutes partially destroys the drug, so solutions should not be sterilized by boiling or autoclaving.

Polymyxin B is bactericidal for many Gram-negative organisms. Therefore, it is indicated whenever a systemic, meningeal, enteric, or local infection is caused by any of the following organisms: *Ps. aeruginosa* (*B. pyocyaneus*); *H. influenzae; A. aerogenes; E. coli; Kl. pneumoniae;* and *Shigella.* It may be administered intramuscularly and intrathecally (to hospitalized patients only), orally and topically.

Polymyxin B was selected from among the available polymyxins because of its relative freedom from toxicity in therapeutic doses. However, in some cases when given the drug parenterally there may be some disturbance of kidney function. This is the reason for this route of administration being used only on hospitalized patients.

Polymyxin B is marketed as Aerosporin by Burroughs Wellcome and Co. (U.S.A.) Inc. The sterile parenteral products are available to hospitals only. The tablets contain 500,000 units each and are available to all pharmacies.

### Aureomycin, Dental

Aureomycin has now been prepared in products specially for dental use. Dental cones, paste and soluble tablets may be used by dentists as an adjunct for the prevention or treatment of bacterial infections commonly encountered in dental surgery. These include necrotizing gingivitis, pericoronitis, acutely infected pulp, acute ab-

scess, periodontal pocket, acute suppurative pulpitis, and periapical abscess, as well as for the prevention of infection following extractions.

Aureomycin crystalline dental cones, dental paste and soluble tablets are marketed by Lederle Laboratories Division, American Cyanamid Company.

**Aureomycin, Surgical**

Aureomycin also has been made available for topical application as an adjunct to surgery. It is designed for use where local antibiotic treatment is desired and is indicated for its action against organisms commonly causing wound infections. Clinical experience suggests that its application to a potentially infected area may materially decrease the incidence and severity of infectious complications.

Lederle Laboratories Division, American Cyanamid Company, are marketing Aureomycin Surgical Powder.

**Bacitracin**

Bacitracin is now being supplied in an isotonic solution containing 500 units per cc. along with cyclomethycaine 0.05 percent. It is indicated for the treatment of the following conditions when caused by bacitracin-sensitive organisms: acute and chronic conjunctivitis, keratoconjunctivitis, blepharoconjunctivitis, meibomitis, secondary infection in trachoma, keratitis, corneal ulcer, marginal ulcer and dacryocystitis. It is also employed prophylactically in therapy when there is a foreign body present. It is dropped directly into the conjunctival fornix of the lower lid. A drop or two several times a day suffices.

The ophthalmic ointment is indicated when a mild antiseptic for external ocular instillation is desired.

The solution known as Bacillyrium and the Bacitracin Ophthalmic Ointment with Phenacaine are marketed by C.S.C. Pharmaceuticals.

**Chloromycetin Palmitate Pediatric**

Chloromycetin recently has been made available in a custard-flavored suspension designed particularly for administration to children. The palmitate form of this antibiotic is used for this purpose since it is tasteless. It is available from Parke, Davis and Co. as a suspension containing Chloromycetin palmitate equivalent to 125 mg.

of Chloromycetin in each 4 cc. (1 teaspoonful) under the title Pediatric Chloromycetin Palmitate.

**Chloromycetin, Parenteral**

There are no acidic or basic groups present in chloramphenicol so that it cannot form salts which are soluble in aqueous vehicles.

It does contain in its chemical structure a dichloracetamide group which led to the investigation of acetamide and the substituted acetamides. It was found that N, N-dimethyl acetamide or acetyl dimethylamine had a good solvent power for the antibiotic. It was possible to prepare a 50 percent solution in a 50 percent aqueous dilution of this solvent and which when added to water or saline solution did not precipitate. The formula finally chosen was 25 percent chloramphenicol in 50 percent of the solvent.

It was found necessary to add the chloramphenicol parenteral solution to the diluent due to the marked affinity for water of the solvent, acetyl dimethylamine. Also it was added as quickly as possible under the surface of the diluent so that the antibiotic would not precipitate on the surface. Diluents which may be used include water, physiologic saline or glucose solutions.

A dry syringe and needle were neceessary to remove the material from the ampul. A minimum of 100 cc. of diluent was reported as necessary to dilute a 2 cc. ampul.

After animal experiments the solution was tested on human subjects. A group of more than 200 individuals was selected for the tests. They varied in sex and in age, from 10 to 50 years. One thousand 2 cc. ampuls were used in the tests. The undiluted solution was given intravenously (using a dry syringe and needle) in doses of 4 cc. (1 Gm. chloramphenicol) to 8 cc. (2 Gm.) as a single injection daily. In order to avoid gastric irritation and a fall in blood pressure resulting from a high blood concentration of the antibiotic, the drug was administered before meals at an approximate rate of 5 seconds per cc.

After each injection there was observed a slight transient rise in temperature and a short period of lowered blood pressure (10-30 mm. Hg.). A few individuals had mild venospasms. Some experienced vomiting after the larger doses, but this was corrected by giving the drug when the stomach was empty. However, there was still a sour or bitter taste noticed in the mouth. An unusual reaction

was a feeling of testicular or vaginal warmth for several minutes after the injection. No sclerosing action on the veins or any phlebitis was observed. However, further investigation is necessary.

Parenteral chloramphenicol is under investigation by Parke, Davis and Co.

**Combiotic P-S**

A combination of crystalline procaine penicillin G, 300,000 units, buffered crystalline sodium penicillin G, 100,000 units, and dihydrostreptomycin (as the sulfate) 1 Gm. is now available.

This combination is effective against pathogens of the Gram-positive and Gram-negative groups. It is recommended for selected cases of bacterial endocarditis, urinary tract infections, including acute gonococcal infections, surgical prophylaxis and in certain infectious diseases of mixed bacterial origin.

Streptomycin alone has no effect on many of the organisms involved and penicillin alone was chiefly bacteriostatic. However, together they are rapidly bactericidal due to the synergistic effect.

This is also marketed in powder form in single dose "drain-clear" vials. Diluent is added to the extent of 2.2 cc. resulting in a volume of 3.3 cc. permitting withdrawal of a full dose of 3 cc.

Under the name of Combiotic P-S Chas. Pfizer and Co. is marketing this combination.

**Compenamine**

Because it has been shown to possess certain anti-allergic properties a new salt of penicillin is being tried clinically. The base, N-methyl-1, 2-diphenyl-2-hydroxyethylamine, was found to possess certain anti-allergic properties not related to any true antihistaminic effect. Therefore, the penicillin salt was prepared and studied. It is prepared as a white powder and distributed in 10 ml. vials. To this is added 4.4 ml. of sterile distilled water, making a total of 5 ml. of penicillin suspension, each ml. containing 300,000 units of penicillin. In powder form it appears to be completely stable. In suspension the stability compares favorably with other forms of penicillin. It is easily administered intramuscularly through a 21 gauge needle and there is practically no discomfort at the time of injection.

Carefully controlled experiments with this new penicillin were conducted on 196 patients. Of these only 5 developed some type of

reaction, making an incidence rate of 2.5 percent. However, of the 5 three were receiving other drugs known to produce reactions, one had a history of a previous severe penicillin reaction, and the last one had a history of a previous nonpenicillin allergic condition which was reactivated.

It is reasonable, therefore, to conclude that the incidence rate is less than 1.0 percent. Thus, this new penicillin salt is indicated for patients known to be sensitive to other forms of penicillin. Although there may be some reaction it will be minimal. It is also possible that the amine base alone may prove of value in bringing about a regression of certain allergic reactions to other forms of penicillin. This remains to be investigated.

Known as Compenamine the new penicillin is marketed by CSC Pharmaceuticals.

**Dia-Discs**

The physician cannot always make an exact diagnosis of a disease so that he can select the proper antibiotic. In many cases also the antibiotic sensitivity of the organism may be unknown. Consequently, there has been developed a set of diagnostic test tablets.

Each small tablet contains a measured amount of antibiotic. In a complete set there is included 24 test tablets of two potencies of the following antibiotics: penicillin, bacitracin, streptomycin, chloramphenicol, aureomycin and terramycin.

The organism in question is streaked over a Petri plate and then the diagnostic tablets are placed on the plate equidistant from each other. They, in turn, produce zones of growth inhibition. These zones of growth inhibition have diameters which are in direct proportion to antibiotic sensitivity. A specially prepared sensitivity chart gives the practical significance of these inhibition zones thus enabling the physician to determine which antibiotic will produce the maximum therapeutic effects. By this method it is not only possible to determine the antibiotic sensitivity of the organism qualitatively but also quantitatively so that very little time is lost in starting proper and specific antibiotic therapy. When so-called therapeutic testing is used much time is lost in determining the proper antibiotic to be used.

The sensitivity chart shown is included with the set of diagnostic tablets as well as a pad of convenient laboratory report slips on which results can be reported.

| | Resistant Organisms | | Sensitive Organisms | | Very Sensitive Organisms | |
|---|---|---|---|---|---|---|
| | Zone Diam. Range* | Test Tube M.I.C.** | Zone Diam. Range | Test Tube M.I.C. | Zone Diam. Range | Test Tube M.I.C. |
| Penicillin 1 Unit | 7 | ⟩3.6 | 8-12 | 0.9-3.6 | ⟩12 | ⟨0.9 |
| Penicillin 10 Units | 7-9 | ⟩7.3 | 10-17 | 1.8-7.3 | ⟩17 | ⟨1.8 |
| Bacitracin 2 Units | 7-9 | ⟩3.1 | 10-12 | 0.8-3.1 | ⟩12 | ⟨0.8 |
| Bacitracin 20 Units | 7-12 | ⟩3.1 | 13-17 | 0.3-3.1 | ⟩17 | ⟨0.8 |
| Streptomycin 10 mcg. | 7-8 | ⟩6.7 | 9-15 | 0.8-6.7 | ⟩15 | ⟨0.8 |
| Streptomycin 100 mcg. | 7-12 | ⟩6.7 | 13-20 | 0.8-6.7 | ⟩20 | ⟨0.8 |
| Chloramphenicol 2 mcg. | 7 | ⟩9.3 | 8-12 | 1.1-9.3 | ⟩12 | ⟨1.1 |
| Chloramphenicol 20 mcg. | 7-10 | ⟩9.3 | 11-20 | 0.6-9.3 | ⟩20 | ⟨0.6 |
| Aureomycin 2 mcg. | 7-8 | ⟩4.9 | 9-12 | 0.6-4.9 | ⟩12 | ⟨0.6 |
| Aureomycin 20 mcg. | 7-10 | ⟩4.9 | 11-16 | 0.6-4.9 | ⟩16 | ⟨0.6 |
| Terramycin 10 mcg. | 7 | ⟩4.1 | 8-12 | 2.0-4.1 | ⟩13 | ⟨0.25-1.0 |
| Terramycin 100 mcg. | 7-10 | ⟩4.1 | 11-17 | 1.0-4.1 | ⟩18 | ⟨0.25-2.0 |

* In millimeters.

** Minimal Inhibitory Concentration in units or micrograms per ml. of medium, developed by serial dilution technique using trypticase soy broth.

Known as Dia-Discs they are available from C. S. C. Pharmaceuticals, a division of Commercial Solvents Corp., New York, N. Y.

**Drilitol**

One of the newer combinations with antibiotics is that containing gramicidin 0.005 percent, polymyxin B sulfate 500 units per cc., thenylpyramine hydrochloride 0.2 percent, hydroxyamphetamine hydrobromide 1 percent and preserved with thimerosal 1:100,000. This combination is indicated in the prophylaxis and treatment of a wide range of common upper respiratory tract disorders, including the common cold and its sequelae, sinusitis, nasopharyngitis, allergic rhinitis, etc. The advantages of this product are that it contains two antibiotics: polymyxin which acts against gram-negative organisms and gramicidin which acts against gram-positive organisms. Their combined anti-bacterial spectrum is extremely wide. Both, furthermore, are not merely bacteriostatic but are also highly bactericidal. Infection, therefore, is obviously controlled much more rapidly than if they were bacteriostatic only. It also contains an efficient antihistaminic, thenylpyramine; and an effective vasoconstrictor.

Under the name of Drilitol this is marketed by Smith, Kline and French Laboratories.

**Feed Supplement**

Both aureomycin and terramycin have been shown to increase the growth of animals and probably of humans. Consequently, they are now being added to animal feeds. The mechanism by which they accomplish this effect is not clear, but it is probably their influence on the intestinal flora favoring organisms producing growth promoting substances.

Bi-Con TM-5 an animal feed supplement containing terramycin is now available from Chas. Pfizer and Co., Inc.

**Fumagillin**

Another new antibiotic is fumagillin. It was isolated from a species of *Aspergillus*. Although it has little antibacterial, antifungal and antiviral activity it does have considerable amebicidal potency. This was shown by *in vitro* tests with *Endamoeba histolytica*.

A crude concentrate of the antibiotic was effective in a dilution of about 1:4,000,000 against *E. histolytica* in the absence of bacteria. Other *in vitro* tests showed that there was no influence on the effectiveness of the antibiotic in the presence of growing bacteria. Thus, the antibiotic must act directly upon the amebae. *In vivo* tests with rats and rabbits have also demonstrated the amebicidal power.

**Neobacin**

A combination of neomycin 10,000 units and bacitracin 2,000 units is being tested in tablet form for the treatment of infantile diarrhea. It was found to cause a significant reduction in the duration of diarrhea, as compared with a control group treated with sulfadiazine, streptomycin, and penicillin alone or in combinations. In addition, no recurrence of the diarrhea was observed in the patients receiving the antibiotic combination.

The average duration of diarrhea in infants treated with the combination including those treated with the combination and procaine penicillin was 3.34 days as compared with 6.44 days in the control group.

It was well tolerated. The tablets were crushed and given with applesauce or jelly. None of the infants developed vomiting and no

other side effects were observed. The new combination was also easily combined with the routine antidiarrheic dietary regimen. No renal damage occurred through the excretion of either antibiotics, as no blood levels from the doses given were obtained in one to four hours after ingestion. Although early administration of fluids and electrolytes is of first importance in diarrhea, the antibiotics do play a role in depressing the intestinal flora and fauna and shortening the duration of the condition so that further disturbances of the electrolyte balance cannot take place.

**Neomycin**

Another antibiotic is Neomycin which is obtained from cultures of the soil organism *Streptomyces fradiae*.

The antibacterial range of neomycin is wider than that of bacitracin, penicillin or streptomycin. It is very active against several Gram-positive and Gram-negative organisms. The sensitizing index is very low even in patients who have other types of allergic dermatitis and in those known to be sensitive to other antibiotics. It is now available in powder, ointment, and ophthalmic ointment forms.

Parenteral injections are not recommended as yet. The ointment is employed as a dressing for burns both to prevent infection or to treat any secondary infections. Either the ointment or the powder in aqueous solution may be applied locally in treating impetigo, sycosis (barber's itch), otitis external, paronychia (infection of skin on the side of the fingernail), herpes simplex (fever blister, cold sores), infected ulcers, infectious eczematoid dermatitis, seborrhea, pustules, pustular acne, and boils. The ophthalmic ointment is indicated in the therapy of infections of the eyelids and the conjunctiva, sties, and marginal blepharitis.

Neomycin has no activity against fungi or true viruses. It is most effective against infections caused by *Proteus vulgaris* and has shown activity against some strains of *Ps. aeruginosa* which were resistant to other agents.

Neomycin is marketed by the Upjohn Co. The ointment forms have been given the trade name Myciguent and contain 5 mg. of neomycin sulfate per gram.

**Neopenil, Leocillin or Estopen**

A new ester-salt form of penicillin, first reported in Denmark about a year ago, has received increasing attention because of its

apparent predilection for lung tissue. It is administered subcutaneously. At first it was found to produce blood levels lower than sodium or procaine penicillin, but then the specificity for lung tissue was discovered. In the lungs it produces concentrations five times higher than either of the aforementioned penicillins. It also has a depot effect lasting as long as 12 hours. It is excreted in considerable quantities with the sputum. Chemically this new penicillin is the hydriodide of the diethylaminoethyl ester of penicillin G. A number of other dialkylaminoalkyl esters of penicillin have been prepared and studied. These esters are not inactivated by penicillinase which is definitely an advantage. They, too, accumulate in the lungs which factor is of value in the therapy of lung diseases.

In Denmark the original "preparation A" or the hydriodide of the diethylaminoethyl ester of penicillin G is known as Leocillin. In England it is available as Estopen from the Glaxo Laboratories, Ltd. In the United States this penicillin is being investigated under the name of Neopenil by Smith, Kline and French Laboratories.

The discovery of the specificity of this product for lung tissue is good evidence that blood level evaluation of various penicillins may be misleading since blood levels may be low when various tissue and organ concentrations may be high.

**Penicillin O**

Penicillin O or the penicillin salt of 1, 2-diphenyl-2-methylaminoethanol is claimed to be hypoallergenic and thus tolerated by penicillin G—sensitive patients. However, some doubt has been cast upon its complete non-allergic effect by the fact that one group has reported that penicillin O was tolerated by only three out of five penicillin G-sensitive patients. Another group found that it caused cutaneous reactions in two of 47 patients with no history of penicillin allergy. Consequently, it is believed that further investigation is necessary to determine the actual extent to which incidence of reaction is reduced.

It has essentially the same antibacterial spectrum as penicillin G when tested *in vitro,* but in some instances it may possess only one-half the potency of penicillin G when assayed by usual methods.

Penicillin O is marketed by CSC Pharmaceuticals and as Cer-O-Cillin by the Upjohn Co.

**Plumercin**

Because the plant genus *Plumeria* often has been described as having certain curative properties and has been used in native remedies the *in vitro* antimicrobial activities of *Plumeria multiflora* have been studied. In India the juice or sap of the *Plumeria rubra* is mixed with sandalwood oil and camphor or with coconut oil and employed in curing the "itch". This particular itch is believed to be the common scabies itch resulting from infestation with *Sarcoptes scabici* and related species. It has also been reported that an exudate of *Plumeria elegans* was responsible for curing pulmonary hemorrhage. An exudate of still another type, *Plumeria holstii,* has been decribed as having styptic properties. *Plumeria bicolor* has been listed as inhibiting *Micrococcus pyogenes* var. *aureus.*

As a result of these earlier studies 103 tropical plant specimens were screened, and it was found that an alcoholic extract of *Plumeria multiflora* possessed considerable activity against *B. subtilis* and *Aspergillus niger* in tests. Therefore, the goal set was the isolation of the active principle and determination of its properties. After a series of extractions the pure plumericin crystallized from benzene. The crystals are colorless lathe or plate-like needles having a melting point with slight decomposition at 212.5-213.5° C., are soluble in chloroform, and slightly soluble in methanol, ethanol, ethyl ether, acetone and benzene but insoluble in petroleum ether and water.

The molecular weight was determined as 290.3. Chemically plumericin is $C_{15}H_{14}O_6$.

In tests of pure crystalline plumericin in strengths of 500 p. p. m. in absolute alcohol this new antibiotic appears to be a rather potent inhibitor of fungi such as *Aspergillus niger, Ceratostomella ulmi, Botritis sp., Trichophyton mentagrophytes, Candida albicans, Penicillium sp., Fusarium exysporium, Stemphylium sp., Alternaria sp.* and *Monilia sp.* It was found to have a smaller degree of activity against the following Gram-positive bacteria: *B. subtilis, B. mycoides, B. megatherium, B. cereus, Sarcina lutea, Micrococcus pyogenes* var. *aureus, Mycobacterium phlei, Mycobacterium avium* and *Mycobacterium tuberculosis 607;* and the following Gram-negative bacteria; *E. coli, K. pneumoniae, Erivinia amylovera, Shigella paradysenteriae, Alcaligenes fecalis, Proteus vulgaris* and *Ps. fluorescens.*

**Streptomagma**

Just introduced is a colloidal alumina gel suspension containing in each fluid ounce 4.63 gr. of dihydrostreptomycin sulfate, 45 gr. of kaolin, and 4 gr. of pectin. It combines all the requisites essential for the prompt and complete clinical remission of infectious bacterial diarrheas.

Known as Streptomagma it is being marketed by Wyeth, Inc.

**Terramycin Otic**

A new dosage form of terramycin consists of a vial containing 25 mg. of crystalline terramycin hydrochloride and a dropper bottle containing 5 cc. of a mixture of 95 percent propylene glycol and 5 percent benzocaine. The two mixed together make a clear solution which remains stable under refrigeration for 48 hours without loss of potency. Thus three actions are combined. The antibiotic destroys infecting bacteria, the benzocaine eases pain and discomfort in the ear, and the propylene glycol softens waxy deposits and relieves congestion. It is indicated in therapy of external ear infections.

Terramycin Otic is marketed by Chas. Pfizer and Co., Inc.

**Terramycin (Veterinary)**

The successful use of terramycin in animals has been reported. It has been used especially in so-called "shipping fever" and pneumonia of cattle and in infections of dogs and cats.

**Tyrolaris**

The first antibiotic mouthwash to be marketed contains tyrothricin, 0.02 percent, d-panthenol, 0.02 percent, and a surface active agent in a 10 percent alcohol base. The tyrothricin acts as a bacteriostatic and the d-panthenol may serve to reduce the number of lactobacilli which are suggested as being partly responsible for dental caries by blocking their utilization of pantothenic acid. The surface active agent promotes spreading and foaming of the solution throughout the oral cavity. It is recommended for general oral hygiene and to lessen the possibility of infection following injury to mouth tissues and dental prophylaxis.

Known as Tyrolaris this mouthwash is available from Sharp and Dohme, Inc.

### Vinactin A

A new species of actinomyces named *Actinomyces vinaceus* has been found to produce at least two different groups of antibiotic substances. A purified preparation of one of these has been found effective in combatting several disease germs in animals, including tuberculosis. In treating tuberculosis in mice the outstanding feature of the antibiotic was reported to be that it was very difficult to develop strains resistant to it, whereas streptomycin quickly develops resistance in the invading organism.

Known as Vinactin A this antibiotic is being investigated by Ciba Pharmaceutical Products, Inc.

## ANTICOAGULANT

### Cumopyran

A new anticoagulant known chemically as 3,4-(2′methyl-2′-methoxy-4′-phenyl)-dihydropyrano-coumarin has been shown to be two to three times as potent as dicumarol. Other advantages of this compound include the following: (a) the action of a specified dose is more predictable; (b) the desired prothrombin level is easier to maintain; (c) onset of action is more rapid; (d) the effect is more prolonged; (e) there is less capillary toxicity; (f) there is little or no gastrointestinal disturbance; and (g) there is much less patient resistance.

Abbott Laboratories have made this anticoagulant available under the name Cumopyran.

### 4-Hydroxycoumarin

4-Hydroxycoumarin has been found to provide more rapidly the desired prothrombin levels than does dicumarol. It is believed to be a better anticoagulant. In 16 percent of the patients tested it produced the desired levels in 24 hours and in 78 percent in 48 hours. The side effects are minimal and the incidence of hematuria is less than half of that resulting in patients given dicumarol.

4-Hydroxycoumarin or No. 63 is being investigated by Abbott Laboratories.

### Heparin

Although heparin has been available for some years, new forms have been reported. It is now marketed in a gelatine-dextrose vehicle

which produces immediate and prolonged anticoagulant action. It has the advantage of subcutaneous injection thus simplifying administrative manipulations. It takes immediate effect and produces a prolonged action lasting about 48 hours.

Anticoagulant therapy is readily employed in ambulatory patients.

The rate of absorption of heparin is under control at all times. The anticoagulant effect may be accelerated by application of heat to the injected site; it may be retarded by similar application of ice; or it may be stopped by prolonged refrigeration, by use of tourniquets, by whole blood transfusions or by globulin injections.

Patient discomfort is reduced to a minimum. Known as Heparin Repository this new form is marketed by Lederle Laboratories Division, American Cyanamid Company, and as Depo-Heparin by The Upjohn Co.

Heparin is considered to be inactive orally. However, recently there have been reports of its use successfully by sublingual administration. A pellet or wafer of 125 mg. of heparin sodium was placed in the sublingual pouch of ten subjects. Disintegration was rapid, and within a half hour the blood clotting time was effectively prolonged. This was maintained for approximately four hours. No side effects were observed.

The workers at Beth Israel Hospital, New York, believe that this sublingual route may well become the method of choice for early anticoagulant treatment of myocardial infarction, pulmonary embolism and thrombophlebitis, and in surgery. This discovery may be of considerable importance in handling soldiers and civilians who are victims for frostbite, for sublingual administration can be started before the victim arrives at the hospital.

One of the most recent uses of heparin is in the therapy of burns and of frostbite. In the case of the former condition it had been shown that heparin did have some beneficial effect on burns, but it was not clear whether survival of the patient might be effected after a massive burn. In animal studies conducted recently it was shown that therapeutic doses of heparin resulted in more than doubling the survival time of the subjects with lethal burns. There did not seem to be any significant difference in survival times between the group given the heparin subcutaneously in an absorption-retarding vehicle and the group given continuous heparinization after the burn had been made. As a result of these studies cautious investigations on burned humans have been begun.

A study of what occurs in the human body when it is frost-bitten has revealed that there is an alteration of the blood circulation, and if allowed to progress eventually there are produced agglutinative thrombi which are not true fibrin thrombi because there are many platelets but little fibrin. As this develops further, and if exposure is continued for several days, the agglutinative thrombi form occlusive red cell thrombi. Consequently, it is recommended that heparin sodium be used to interrupt the developing process. In addition to its interference with the adhesiveness of the agglutinative thrombi, thus preventing thrombosis and gangrene in acute frost-bite, heparin also preserves the reabsorption power of the interstitial fluid. Thus secondary fibrous tissue formation is prevented. As a result the blisters have no clots formed in them. However, for the anticoagulant therapy to be effective it must be given within at least 16 hours after exposure and preferably before that. It is necessary too that the drug be given in effective and adequate amounts.

A recent report of patients with frostbite confirmed this. Of 14 patients only one required local amputation of a finger. Not only was the period of hospitalization reduced, but also the patient was able to resume normal activities more quickly.

Dicumarol, too, has shown value in treating frostbite.

### Treburon

Treburon, a new synthetic anticoagulant, has been reported to have an activity of approximately one-fourth to one-half that of heparin by intravenous and intramuscular routes. The toxicity is about one-half that of heparin. It is partially excreted in the urine. No spontaneous hemorrhages were produced in subacute toxicity tests and no adverse effects were observed on the growth of the blood picture. It is being studied by Hoffman-LaRoche, Inc.

## ANTICONVULSANT

### Prenderol

D.E.P. or 2, 2-diethyl-1, 3-propanediol is a new convulsant related to Mephanesin. When tested on animals and compared with Metrazol, strychnine, and electric shock it exerted a selective depression on multisynaptic neurone arcs in the spinal cord.

Under the trade name Prenderol it is available from E. R. Squibb and Sons.

## ANTI-INFECTIVES

### Asterol Dihydrochloride

A new antifungal agent known chemically as 2-dimethylamino-6-(diethylaminoethoxy)-benzothiazole has produced cures in 60 percent of 83 cases of ringworm of the scalp. It also has shown value in treating other infections caused by fungi. The *in vitro* tests of this drug revealed its fungistatic action.

In the clinical trials it has shown greater effect than any other agent employed by the investigators.

The organism responsible for the 83 test cases included *M. audouini* (61), *M. lanosum* (21) and *T. gypscum* (1). Thirty-four of the 61 cases caused by *M. audouini* were cured, 14 improved and 4 responded to therapy. Consistently negative results have been found in nine others who have not completed the course of six examinations. Sixteen of the 21 caused by *M. lanosum* were cured; four others showed negative examinations but were not considered completely cured; one showed improvement. Improvement was observed also in the one case due to *T. gypseum*.

In fungal infections of the glabrous skin of the nails administration of the new drug twice a day for four to six weeks caused improvement in 57.1 percent of the cases. Two experienced inflammatory reactions. Thirteen of 22 patients with ringworm of the groin, perineum and perianal region were cured and eight showed improvement. One did not change. *C. albicans* was the cause of this condition in four cases and all were cured.

Known as Asterol Dihydrochloride this fungicidal agent is marketed by Hoffmann-LaRoche, Inc.

### Dimethylguanidine

The research for an effective cold therapy preparation still continues. Recent reports have shown that another combination has shown possibilities in treating the common cold. It consists of dimethylguanylguanidine hydrochloride, also known as Flumamine, and sodium sulfathiazole. Satisfactory results have been achieved in both humans and chickens. In colds ranging from simple coryza to chronic sinusitis 95 percent recovery was obtained in the 200 cases. A dosage of 1 cc. of the combination contains 0.015 gram of Flumamine and 0.025 gram of sodium sulfathiazole. Following this dose

headache will disappear in ten to fifteen minutes, to be followed with gradual dryness of the nasal mucous membrane in a just beginning coryza. In chronic cases, an average series of six injections of one cc. daily to the deltoids will produce recovery from all clinical symptoms.

This therapy has rationale because of the antiviral and antihistamine action of Flumamine plus the antibacterial action of sodium sulfathiazole.

**Ethyl Vanillate**

Histoplasmosis is a severe systemic fungus infection of the reticuloendothelial system, characterized by ulcerations of the oropharynx and gastrointestinal tract, and commonly accompanied by hepatomegaly, splenomegaly, and lymphadenopathy. In many thousands of individuals it produces pulmonary calcifications without symptoms. In children this disease usually causes death in a few weeks or several months and in adults from five months to two years. The benign form is to all appearances nonprogressive.

Because there are no specific drugs for this condition therapy is symptomatic. Recently, ethyl vanillate has been shown to have some effect on the causative organism, *H. capsulatum*. Chemically it is 4-hydroxy-3-methoxy-benzoate and is produced by the paper industry as a by-product in the manufacture of sulfite pulp. It is capable *in vitro* of inhibiting the growth of *H. capsulatum* organisms in concentrations of 20-30 mg. per 100 cc. Although this concentration is relatively high it does come within the range of levels which can be safely developed in human tissue and body fluids. The difference between the therapeutic level and toxic level amounts to only 25-30 percent.

Ethyl vanillate is extremely potent and may burn the mucosa of the mouth and irritate the stomach. However, if given in capsule form to adults most of this effect is avoided. Since most of the cases studied were young children it was administered in a 40 percent concentration in olive oil. Although the drug does separate from the oil after being swallowed it was believed that gastric irritation was prevented.

The 12 patients treated included those with varying degrees of this disease. Of the five who now have been well for one to 18 months it is possible that one or two might have survived but not all five could have.

There were three cases of rash and one patient showed a transient elevation of the temperature after therapy was discontinued. In two patients respiratory alkalosis occurred.

Although the toxic effects of ethyl vanillate appear to be great, the fact that some patients were cured by its administration is certainly promising and should lead to further investigation of this drug in the therapy of severe histoplasmosis.

### Selsun Suspension

An orange-colored liquid suspension of 2.5 percent selenium sulfide has been prepared. It contains sufficient detergent for ease of application and rinsing. It is indicated in the treatment of seborrheic dermatitis and common dandruff. It has proven very effective in clinical trial. It is available from Abbott Laboratories.

### Thiocarbarsone

The arsenicals have been used for many years in the treatment of various diseases. Recently a new one has been developed which is indicated for all forms of intestinal amebiasis. Chemically it is 4-carbamidophenyl di-(carboxymethylthio) arsenite. It provides 19.1 percent available arsenic in trivalent form. Clinical studies have proven its effectiveness in clearing of the infection approximately 90 percent of the cases. It should not be administered for amebic hepatitis or in the presence of impaired liver or kidney function.

Under the trade name Thiocarbarsone this arsenical is marketed by Eli Lilly and Co.

## ANTIMALARIALS

### Primaquine and Isopentaquine

Primaquine and isopentaquine were first synthesized in 1945. Because both of these antimalarials seemed to have similar effects the latter was selected in 1948 for clinical trials. It was shown to be effective in 95 percent of all cases of malaria relapse.

Later attention was again focused on primaquine and it is now believed to be the most effective drug. It does not produce a cure after one administration by any means. It is given under a physician's care for 14 days. Best effects are obtained when it is given

in conjunction with quinine. Thirty-two of thirty-three patients given primaquine and quinine suffered no relapses.

In comparison tests primaquine has been shown to be, weight for weight, four times as effective as any of the other antimalarials. In addition the toxicity is low, for ten times the curative dose can be given without any fatality.

### 50-63

One of a series of aryldiaminopyrimidines (ADP's) has been shown to have high antimalarial potency. Chemically it is 5-*para*-chlorophenyl-2, 4-diamino-6-ethylpyrimidine and is known in the laboratory as 50-63.

Because of its high potency and moderate cost, it may eventually bring relief to large native populations never before treated.

The new antimalarial resulted from fundamental studies on the role of nucleic acids in cell multiplication, which studies have been carried out for the past eight years. Substances which interfere with a variety of disease-producing tissues and organisms have been found during this long term project but have not reached the state of development of the new antimalarial agents. Further investigations are being conducted on this drug by Burroughs, Wellcome and Co. (U.S.A.) Ltd. If it successfully passes the remaining hurdles its moderate cost and high potency may bring it into wide usage. The drug presumably is of the suppressive type and may be particularly adapted for use in areas where malaria is endemic and treatment must be continuous.

Synthesized from readily available materials and required in only small amounts, the new drug may well provide an unusually valuable weapon with which to fight malaria on new fronts.

## ANTISEPTICS

### PVP Enhances Iodine Activity

One of the drawbacks to iodine as a topical germicide always has been its toxicity. In the past year tests have been made of a combination of iodine and polyvinylpyrrolidone (PVP). It was reported that the combination is more effective than iodine alone in the therapy of bacterial infections, because the effects last longer; it is practically non-irritating and can be used on all tissues without danger of burn or intense irritation.

The combination is much less toxic than iodine alone and in the clinical trials thus far has not produced any iodine sensitivity. PVP is a white powder which, when dissolved in water provides a clear solution. It not only reduces the toxicity of iodine, but also increases its effectiveness against bacterial organisms and viruses.

When first developed PVP was tested for its prolonging effect on insulin, penicillin and cortisone. When given with insulin PVP was found to reduce the use of this substance from three daily injections to one every other day. It also has been used as a substitute for blood plasma, but not for whole blood in cases of shock and dehydration.

PVP is manufactured by General Aniline and Film Corporation.

## ANTISPASMODICS

### Hexamethonium Bromide

Hexamethonium bromide or C6 is a new gangliomic blocking agent which shows value in the clinical evaluation of the sympathetic vasoconstrictor component in cases of peripheral vascular disease, as well as in the treatment of acute peripheral vascular disorders associated with neurogenic vasospasm. The duration of action of a 50 mg. dose is one to two hours. It can be given by all parenteral routes but is not effective orally or sublingually. Patients to whom it was given showed marked increases in digital blood flow and skin temperature without inhibition of digital reflexes. The increase in skin temperature was greater and more lasting than that following administration of Priscoline and tetra-ethyl ammonium chloride. Side effects were also at a minimum except for severe postural hypotension.

This drug is supplied by E. R. Squibb and Sons as Bistrium Bromide.

### Bentyl Hydrochloride

The chemical, β-diethyl-aminoethyl-1-cyclohexanecarboxylate hydrochloride, has been shown to possess certain antispasmodic properties.

Because of these effects it has been tried clinically in the symptomatic therapy of functional digestive diseases and primary dysmenorrhea. The dosage employed was 10 to 20 mg. three times a day.

When given to 111 patients for periods varying from one to ten months the drug was found to cause no undesirable side effects as is the case with some antispasmodics.

Manifestations of smooth muscle spasm were associated with the irritable colon syndrome, dysmenorrhea, ulcerative colitis, diverticulitis, duodenal ulcer, gastric ulcer, intestinal obstruction, cancer of the digestive tract and gall bladder disease. Included among the symptoms were pain in the abdomen, spastic constipation, diarrhea, abdominal cramps, nausea, regurgitation, rectal pain and tenesmus.

Of the 111 patients, 71 were studied so thoroughly that therapeutic evaluations could be made. Almost complete symptomatic relief was obtained in 36 and partial but satisfactory relief in 24 others. Little or no relief of the spasm was experienced by the 11 remaining patients.

This new antispasmodic has been given the generic name, dicyclomine hydrochloride and as Bentyl Hydrochloride is combined with aluminium hydroxide gel, magnesium oxide, sodium lauryl sulfate and methyl cellulose and marketed as Kalantyl by the Wm. S. Merrell Co.

## ANTITHYROID DRUG

**Itrumil**

The sodium salt of 5-iodo-2-thiouracil is now being used as an antithyroid drug. The iodine in the compound is organically incorporated in the thiouracil molecule. This compound not only inhibits the formation and/or secretion of thyroxine and thyroglobulin (antithyroid effect) but also the activity of thyrotrophin on the thyroid (antigoitrogenic effect). Thus far this compound is believed to be the only thiouracil derivative which inhibits thyrotrophin.

The following advantages are claimed for this new thiouracil compound: (a) Effective antithyroid action practically without goitrogenic effect. This is particularly important in treating hyperthyroid patients who have large goiters which give rise to pressure symptoms. Other thiouracil derivatives may cause increase in gland size.

(b) Vascularity and friability of the hyperplastic gland are reduced, thereby facilitating thyroidectomy and decreasing operative risk.

(c) No adjunctive iodine therapy is required.

(d) The incidence of side effects with this therapy is lower than with any other member of the thiouracil family.

(e) Hypothyroidism apparently cannot be produced by prolonged use of therapeutic doses of this drug in the long-term medical management of thyrotoxicosis.

Known as Itrumil this drug is marketed by Ciba Pharmaceutical Products, Inc.

## ARTHRITIS

### Plasma Therapy

Within the past year the effect of postpartum plasma in the treatment of rheumatoid arthritis has been described. The plasma was taken from mothers 48 hours after childbirth and administered to seven patients who had been crippled, some helplessly so, for years. As a result of this therapy, the patients were able to go through a series of calisthenics including rope jumping.

The postpartum plasma appears to have a long-lasting effect (24 months) without remission in contrast to ACTH or cortisone which effects wear off in several days or weeks. In addition the patient does not need to be hospitalized. Thus far no side effects have been reported. Still another advantage is the availability of the plasma and its relative inexpensiveness.

## ASTRINGENT

### Aluminum Methane Disulfonate

A new astringent has been synthesized. Chemically it is aluminum methane disulfonate (aluminum methionate). In experiments it has shown more astringent effects than other commonly used astringents; it is harmless to fabrics and is very soluble, hydroscopic and non-toxic. The hydroscopic effect prevents creams containing it from drying out and hardening.

## BLOOD AND PLASMA SUBSTITUTE

### Okra

The need for blood plasma is always increased in time of emergency and scarcities always spur on the search for substitutes. Thus

a new substitute has been reported as obtained from the garden vegetable, okra. It appears to have all the advantages and none of the disadvantages of blood plasma. It can be made in powder form and to make the equivalent of a quart of human plasma less than an ounce need be added to a quart of normal saline solution. It does not contain any of the harmful elements which cause side effects as plasma does.

The powder can be stored indefinitely and at any temperature. It is much less expensive than plasma and can be stored in less space. However, there is considerable controversy concerning this product and at present it is strictly on an experimental basis.

## CURARE ANTAGONISTS

### Tensilon Chloride

The development of a new, potent curare antagonist which acts within one-half to one minute, has been announced. Chemically it is (3-hydroxy-phenyl) dimethylethyl ammonium chloride. It is useful whenever a curare antagonist is needed either to terminate the action of curare when no longer required or to counteract overdosage. It is particularly valuable in abdominal and pelvic surgery, in endoscopy, in shock therapy, in patients whose muscle spasm is under treatment with curare, and in other conditions in which curare is used. It is a potent antagonist for d-tubocurarine, Flaxedil and dimethyltubocurarine (Metubine or Mecostrin), but is ineffective against Syncurine and Mytolon.

Known as Tensilon Chloride this drug is available from Hoffmann-LaRoche.

## DENTAL AIDS

### Bacitracin and Gelatin

A combination of bacitracin and an absorbable gelatin sponge has been used to prevent infection and postextraction hemorrhage in more than 1,000 dental patients. Bacitracin is used because it has a wide antibacterial spectrum and is not inhibited by any enzyme. The gelatin sponge controls bleeding and aids clot formation, thus promoting healing.

The gelatin sponge is cut in the desired size and placed in a jar to which is added 5-2 cc. ampuls of procaine solution and 10,000 units

of dry bacitracin. The absorbable gelatin sponge used is Gelfoam marketed by the Upjohn Company.

## DIABETIC AIDS

### Insulin Structure

One of the important announcements at a recent meeting was the fact that the partial chemical structure of insulin had been determined.

By assuming a molecular weight of 12,000 and by using 1, 2, 4-fluorodinitrobenzene it was found that bovine insulin possesses four free alpha amino groups per molecule, indicating insulin has four open peptide chains. Two of the free amino groups are located on glycine residues and two on phenylalanyl residues. The polypeptide consists of four peptide chains joined by 6-S-S-bridges of the cystine residues.

There are two fractions formed after splitting the sulfide bridges of the dinitrobenzene derivatives. The A fraction is believed to consist of glycine N-terminal residues and has 21 amino acid residues and four sulfur atoms per chain. Acids proved to be absent from the A fraction were lycine, arginine, histidine, tyrosine, phenylalanine and proline.

Fraction B consists of phenylalanine N-terminal residues and has 30 acid residues and two sulfur atoms per chain. It has been proposed that the sequence of amino acid residues in the B fraction of insulin is phenylalanine, valine, aspartic acid, glutamic acid, histidine, leucine (cystine-S), glycine, serine, histidine, leucine, valine, glutamic acid, alanine, leucine, tyrosine, leucine, valine (cystine-S) glycine, glutamic acid, arginine, glycine, phenylalanine, tyrosine, threonine, proline, lycine, alanine.

## DIAGNOSTIC AIDS

### Gutta Test Minor

A new laboratory test for urinary albumin and sugar is now available. The entire test takes only 60 seconds compared to as much as ten minutes required by other procedures. With this test there are no test tubes, no Bunsen burners and no messy equipment to clean up. Just one drop of urine and one drop of Gutta reagent and the test is complete. No heat is required to test for sugar.

The reagents are unconditionally guaranteed for one year for validity. A check solution is supplied with each kit to periodically ascertain the reagents' validity and also to familiarize the doctor or technician with the appearance of positive findings.

Gutta Test Minor is available from Biochemical Methods, Inc.

**Monophen**

A modern cholecystopaque which reduces to a minimum the cramps, diarrhea, nausea and vomiting heretofore associated with cholecystographic procedure has been developed. Chemically it is 2-(4-hydroxy-3, 5-diiodo-benzyl)-cyclohexane carboxylic acid and contains 52.2 percent iodine in stable combination. It has been used in more than 3,000 cases and complete diagnostic confirmation was obtained in those cases where surgical intervention was recommended.

National Synthetics, Inc. is marketing this product under the name Monophen.

**Tests for Cancer**

A new "papain washing technic" is reported to be of value in diagnosing stomach cancer at an early curable stage. Cancerous tissues generally shed cells in the hollow organs of the body, but in the stomach the cells either are held in the mucus which coats the lining or are destroyed by the digestive juices. However, by washing the stomach with a papain solution a sample of the stomach wall cells can be obtained. The solution is removed from the stomach with a syringe. Papain dissolves the mucus and carries the cells along with it.

A new synthetic substance when mixed with blood serum reveals the presence of cancer in 98 percent of the cases. The substance is prepared from the bile fraction, desoxycholic acid. Until it was synthesized only a small amount was available because it was obtained from the liver of patients who had died of cancer.

When this substance is mixed with the serum of a cancer patient the serum flocculates. This does not occur in non-cancerous patients. It was suggested years ago that cancer is produced in the body by a natural substance present in the liver and other tissues, which is eliminated in normal persons but is allowed to accumulate over the course of years in persons who develop cancer. This substance causes the production of antibodies which hold it in check for a time until

their production is so decreased that control is impossible. Thus the antibodies present in the serum of a cancer patient coagulate the carcinogen when it is added to the serum in the test.

**Evans Blue Dye**

Evans Blue Dye is an azo dye first synthesized in the late 19th century. It is used to determine blood volume and how much blood is required for a transfusion. It also has been used experimentally to determine the efficiency of the heart, to spot abnormal openings between its various chambers, to evaluate "blood substitutes," to study the permeability of various tissues when acted on by drugs, to trace the spread of certain infections, to measure the amount of oxygen in blood, to determine how long it takes the blood to circulate, to evaluate work done by the heart, and to localize abscesses and malignant growths. If there is severe shock or congestive heart disease the dye will require 15 minutes to mix with the blood whereas if the patient is normal only 9 minutes are required. This dye is now available in a form, suitable for the practicing physician, from Warner-Hudnut, Inc.

**Telepaque**

A new cholecystographic medium has been prepared which gives adequate visualization with minimum toxic effects. Its chemical formula is 3-(amino-2,4,6-triiodophenyl)-2-ethylpropanoic acid and contains 66.68 percent iodine. It is being studied for clinical use. Tested on cholecystograms in animals it has been found to give a shadow density equal to or greater than that obtained with iodoalphionic acid. Thus far no side effects have been observed. Its toxicity is only one-third that of iodoalphionic acid, and it is easily administered.

Winthrop-Stearns are studying this new medium under the tradename of Telepaque.

**(To be concluded in next issue)**

# ENZYME-VITAMIN TEAM

## *aids digestion...*
## *supplements nutrition*

**TAKA-COMBEX** is especially useful when caloric needs and vitamin requirements are highest—in illness and convalescence, pregnancy and lactation, in the very young and the very old.

It provides physicians with a combined digestive aid and nutritional supplement in convenient Liquid or Kapseal® form.

**The vitamins** assure patients adequate intake of important factors of the B-complex (C also, in the Kapseals). In addition, the B-vitamins are essential in carbohydrate metabolism.

**The enzyme,** Taka-Diastase,® is one of the most potent starch digestants known. It also enhances absorption of vitamin B.

# TAKA-COMBEX Liquid Kapseals

*vitamin supplement and starch digestant*

### TAKA-COMBEX Kapseals

*Each Kapseal contains:*

| | |
|---|---|
| Taka-Diastase (*Aspergillus oryzae* enzymes) | 2½ gr. |
| Vitamin $B_1$ (Thiamine Hydrochloride) | 10 mg. |
| Vitamin $B_2$ (Riboflavin) | 10 mg. |
| Vitamin $B_6$ (Pyridoxine Hydrochloride) | 0.5 mg. |
| Pantothenic Acid (Sodium Salt) | 3 mg. |
| Nicotinamide (Niacinamide) | 10 mg. |
| Vitamin C (Ascorbic Acid) | 30 mg. |

With other components of the Vitamin B Complex derived from liver.

In bottles of 100 and 1000.

### TAKA-COMBEX Liquid

*Each teaspoonful (4 cc.) contains:*

| | |
|---|---|
| Taka-Diastase (*Aspergillus oryzae* enzymes) | 2½ gr. |
| Vitamin $B_1$ (Thiamine Hydrochloride) | 2 mg. |
| Vitamin $B_2$ (Riboflavin) | 1 mg. |
| Vitamin $B_6$ (Pyridoxine Hydrochloride) | 0.5 mg. |
| Pantothenic Acid (Sodium Salt) | 2 mg. |
| Nicotinamide (Niacinamide) | 5 mg. |

In 16-ounce bottles.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY

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The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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